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ABSTRACT

In this study of young male schizophrenic patients who reported they were not taking antipsychotic medication at follow-up, those treated with placebos in contrast to those treated with chlorpromazine while hospitalized showed significantly greater long term clinical improvement, less pathology at follow-up, fewer rehospitalizations and better overall functioning in the community between one and three years after discharge. These individuals, in general, were experiencing an acute psychotic break and their first or second hospitalization upon admission to the study. Between hospital admission and discharge those on chlorpromazine showed greater improvement. A greater proportion of those who were assigned to chlorpromazine while hospitalized, however, showed deterioration after discharge. Factors measured at hospital admission that were related to post-hospital outcome were good premorbid history and paranoid characteristics. One evoked potential criterion, slope, also was found to be related to outcome. Similarities and differences between this and other drug outcome studies were discussed. The study supports previous observations that there is a subgroup of schizophrenics who do well or better long term without the routine or continuous use of antipsychotic medication. This finding underlines the need for more selective utilization of antipsychotic medication. Factors which may have an effect on the successful management of acute schizophrenic patients not on medication are mentioned. (Author)

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# Schizophrenics for Whom Phenothiazines May Be Contraindicated or Unnecessary

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SUMMARY

In this study of young male schizophrenic patients who reported they were not taking antipsychotic medication at follow-up, those treated with placebos in contrast to those treated with chlorpromazine while hospitalized showed significantly greater long term clinical improvement, less pathology at follow-up, fewer rehospitalizations and better overall functioning in the community between one and three years after discharge. These individuals, in general, were experiencing an acute psychotic break and their first or second hospitalization upon admission to the study. Between hospital admission and discharge those on chlorpromazine showed greater improvement. A greater proportion of those who were assigned to chlorpromazine while hospitalized, however, showed deterioration after discharge. Factors measured at hospital admission that were related to post-hospital outcome were good premorbid history and paranoid characteristics. One evoked potential criterion, slope, also was found to be related to outcome. Similarities and differences between this and other drug outcome studies were discussed. The study supports previous observations that there is a subgroup of schizophrenics who do well or better long term without the routine or continuous use of antipsychotic medication. This finding underlines the need for more selective utilization of antipsychotic medication. Factors which may have an effect on the successful management of acute schizophrenic patients not on medication are mentioned.

# Schizophrenics for Whom Phenothiazines May Be Contraindicated or Unnecessary [1)]

BY MAURICE RAPPAPORT, H. KENNETH HOPKINS, KARYL HALL, TEODORO BELLEZA, AND JULIAN SILVERMAN

For most schizophrenics antipsychotic medication is the treatment of choice. A number of investigators and clinicians have observed, however, that some schizophrenics do better or get along quite well long term without the use of antipsychotic medication (Silverman, 1972) (Silverman, 1974) (Sullivan, 1953) (Dabrowski & Aronson, 1964) (Goldberg et al, 1965) (Kraepelin, E, 1913) (Lehmann, 1967) (Menninger, 1959) (Mosher et al, 1974) (Goldstein, 1970) Perry, 1962) (NIMH Study, 1964). Reports also indicate that phenothiazines may have less than helpful and sometimes paradoxical effects on some patients. For example Goldberg (1965) reports that patients observed to be "not irritably resistive" improved to a greater extent on placebos than on chlorpromazine. Hollister (1964) found that "insightful" patients when given phenothiazines, often showed an exaggeration of schizophrenic symptoms. Goldstein et al (1969, 1970) reported that under the influence of phenothiazine medication increased indications of thought disorder occurred in acute, nonparanoid schizophrenics with good premorbid histories; with placebos decreased indications of thought disorder occurred. Magaro and Vojtisek (1971) found that among acute reactive nonparanoids receiving phenothiazines perceptual differentiation was significantly more impaired. Sarwer-Foner (1960) has described personality characteristics of patients in whom he noted that chlorpromazine produced an intensification of their psychopathology. He suggested these

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individuals had an increased need for psychomotor activity and acting out relationships and these needs were threatened by drugs with sedative effects. Heninger, Dimascio and Klerman (1965) generally supported the interpretations of Sarwer-Foner. Hogarty, Schooler and Goldberg (1973) have recently mentioned finding a subgroup of schizophrenics who do well long term without antipsychotic medication.

If it is true that phenothiazines and other antipsychotic medication may not be necessary for certain kinds of schizophrenia and, in fact, their constant long term use may be contraindicated in some instances, then it becomes a challenge to learn for whom they are and for whom they are not indicated and how these medications may be used more selectively and appropriately.

An examination of the literature suggests that schizophrenics likely to have a relatively good prognosis (that is, able to sustain themselves reasonably adequately in the community) are those who have a good premorbid history, who have experienced an acute psychotic break rather than a slow, insidious onset of schizophrenia, and who have not exhibited chronic and deteriorating schizophrenia. (Straus and Carpenter, 1974) (Evans, Goldstein and Rodnick, 1973) (Vaillant, 1964) (Zigler and Levine, 1973) (Bromet et al, 1974) (McCabe et al, 1972).

There is controversy, however, about how paranoid symptomatology related to prognosis. There are reports which indicate that some paranoid schizophrenics with good premorbid histories have a reasonably good prognosis, particularly when their paranoia is limited or circumscribed (Strauss, Sirotkin and Grisell, 1974) (Freedman, Cutler et al, 1967). On the other hand Goldstein (1970), Judd et al (1973) and Evans et al (1973) indicate that prognosis is better, in general, for nonparanoid schizophrenics with good premorbid histories. Silverman has also postulated that a nonparanoid "prototype" has a better prognosis than a paranoid "prototype" schizophrenic (personal communication). He defines his prototypes in neuropsychological terms. Basically Silverman has postulated that schizophrenics who show an attenuation or reduction of certain elements of the cortical evoked potential in

response to stimuli of increasing intensity ("reducers") are showing a particular style of perception and information processing that is related to paranoia and clinical outcome.

In this study clinical outcome was examined in young schizophrenics while hospitalized after the onset of an accute schizophrenic episode and also for up to three years after discharge from the project taking into account their premorbid history and their paranoid-nonparanoid clinical characteristics as well as the "reducer" or "augmenter" perceptual styles they displayed at admission. Of particular interest was the opportunity to examine differences in short and long term outcome between groups who were found to be off antipsychotic medication at follow-up but who, while hospitalized, had been assigned randomly to either a placebo or chlorpromazine medication condition.

SUBJECTS, PROCEDURES AND MEASURES

Data were obtained on 127 young male acute schizophrenics while they were residents of Agnews State Hospital (San Jose, California). Patient characteristics are shown in Table 1. At admission to the project 59% (74) were found to be free of medication. Lengths of hospitalization after admission to the project in relation to assigned medication conditions are shown in Table 2.

Post-hospital clinical information was obtained for 81 patients (64% of those who participated in the hospital phase of the study) followed through personal contact up to 36 months after discharge from the project. Information, particularly rehospitalization information, on an additional 27 patients was obtained primarily through mail or contact with significant others. Consequently, partial follow-up information was obtained on 108 subjects - 85% of those in the study. The lengths of time different numbers of patients were in the follow-up phase, the number of rehospitalizations they experienced, their place of residence and their employment status at last contact are shown in Table 3.

A comparison was also made of the number of those with good and poor premorbid histories and paranoid or nonparanoid diagnoses in both the follow-up and total project samples. The proportions were virtually identical.

Patients selected for the project had to meet the following criteria: be between 16 and 40 years, have no allergy to chlorpromazine, have had no electroshock therapy within six months preceding admission, have no gross organic impairment, no history of epilepsy and no known history of drug abuse prior to admission and no or few previous hospitalizations.

Patient Assessment: On the day of admission to the project a patient was acheduled to receive a physical and mental status examination. On that day or the day following (Day 2) two trained research personnel also interviewed each patient and completed a modified form of the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham), a Global Assessment (GA) Rating Scale, a premorbid history form based upon Kantor's Process-Reactive Criteria (1966) / and a paranoid-nonparanoid form based upon the Venables & O'Connor scale (1959). At discharge the administration of the BPRS and GA scales was repeated. Nursing staff completed the Nurses Observation Scale for Inpatient Evaluation (NOSIE).

Clinical measures included the following:

a. Severity of Illness (SI). This is a composite of the following measures the first three of which are based upon BPRS items:

   1) Overall Thought Disturbance (OTD)

   2) Overall Emotional Disturbance (OED)

   3) Overall Functional Disturbance (OFD)

   4) Global Assessment (GA)

   5) Nurses Observation Scale for Inpatient Evaluation (NOSIE)

   All patient scores for each measure were ranked, divided into quartiles and designated as scores of 0, 1, 2 and 3 with 0 indicating no psychological

illness or disturbance and 3 indicating extremely severe psychological illness or disturbance. The scores were added together and averaged for each subject. This yielded severity of illness scores ranging between 0 and 3. For this report the days of primary interest are at admission (Day 2), at discharge and at last follow-up contact.

Personnel were trained to complete the BPRS by observing and later by conducting interviews in the presence of the principal investigator (MR). In addition six video tapes of interviews with schizophrenic patients were presented. Interviewer ratings were compared with "master" ratings made by three experienced interviewers who previously had interviewed the patient appearing on the video tape (at the same session at which the taping was done). Discrepancies in ratings were discussed prior to the next training tape being shown. Generally it was found after training that raters did not usually differ by more than one point on seven point rating scales.

b. Clinical Change Index (CI). This is the change in clinical status overtime that was obtained by recording improvement or worsening (as a plus or minus score respectively) that occurred between Day 2 and discharge from the project (CI 2 - DIS) as well as between Day 2 and last follow-up contact (CI 2 - FU) and between discharge and last follow-up contact (CI DIS. - FU). The direction of change was recorded for each measure and divided by the number of measures available. This yielded scores ranging between +1.00 (improved on all scales) through 0.00 (no change) to -1.00 (worse on all scales). Directions of change rather than actual scores were used so that data would be comparable across different clinical measures.

Pharmacological. Urine samples were obtained at admission to the project and at scheduled intervals and tested for phenothiazine metabolites using the FPN test of Forrest. (Forrest et al, 1961). These data were used to determine

whether or not patients upon admission to the hospital were off or on phenothiazine medication. In addition the test was used subsequently to confirm that patients assigned to the placebo condition remained free of phenothiazines whether those assigned to chlorpromazine were taking it.

The individual conducting the FPN tests did not participate in completing psychological and behavioral rating forms. Ward staff, raters and all other research personnel remained blind to the drug condition of patients. Periodically staff were asked to guess whether patients were on chlorpromazine or placebo. Quite consistently 40 to 50% of the time wrong guesses were tallied indicating staff were essentially blind to the patients' actual drug status most of the time.

Medication All patients took nine tablets a day (three, three times a day). Those assigned to the chlorpromazine condition received a minimum 300 mg a day. The physician could order up to 900 mg of chlorpromazine a day but he too remained blind as to whether the patient was receiving medication or placebos. At times non-blind medication intervention was necessary on a temporary basis. Specifically, temporary medication intervention consisted usually of giving the patient a barbiturate first in an effort to calm or sedate him with a drug that would be quickly metabolized and that would not have a prolonged effect. Prolonged non-blind medication intervention (i.e., five days or greater) was cause for terminating a patient's participation in the study. Seven individuals were terminated from the study for this reason. Two others were terminated because of allergy to chlorpromazine. As experience was gained in handling acutely disturbed psychotic individuals the number of such interventions decreased. 76 required no intervention, 21 required one or two interventions and 11 required three to six interventions. Most interventions occurred among those on placebos (36 patients, 49% of those on placebos) as compared to those on medication (15 patients, 28% of those on chlorpromazine).

Follow-Up Follow-up measures consisted of GA and BPRS ratings obtained, whenever possible, at 1, 3, 6, 12, 18, 24, 30 and 36 months after discharge from the hospital portion of the project. Ratings were made by a trained research assistant who was blind to what the patient's medication condition was while he was hospitalized. A patient's medication status at follow-up was determined by asking the patient whether he was on tranquilizer medication at the time he was being interviewed and also by checking his medication usage with a significant other, if one was available. Data from last follow-up contacts only are analyzed in this report.

Visual Evoked Potentials (VEP) and Measurement of Reduction and Augmentation. Subjects were seated in an upright position in a comfortable recliner chair with their heads located approximately 6 inches in front of a 12" square opening into a 21" x 21" x 21" box lined with crinkled tinfoil which reflected light flashes (source not visible to the subject). This apparatus and the subject remained in a completely darkened acoustical room (IAC, Model 404A) throughout the testing period. Subjects were instructed to relax and observe the light flashes with eyes open. A research assistant stayed in the room with the patient to make sure he remained alert and sat quietly with minimum movement.

Silver-silver chloride electrodes (Grass Instruments Company) were attached to the scalp at the vertex position and to both ear lobes (right ear used as ground) with Bentonite paste after scalp and skin were cleaned with rubbing alcohol. Resistance was maintained under 10K ohms. Electrical potentials were amplified by cascaded pre-amplifiers (Tektronix, Model 122) with an overall gain of about 25,000 and a bandwidth of from 1 to 70 hz. Calibration of the VEP measure was undertaken daily using a precision pulse generator.

Subjects were presented a randomized sequence of 120 light flashes at each of four intensities (9, 34, 138, 420 lux, where one lux is equal to one lumen per

square meter of surface). Flashes were of 15 msec duration and were presented at a rate of one flash per 1.1 seconds. A testing session lasted nine minutes. Light sources were four florescent lamps (Model F8T5/CWX, Sylvania Electric Company) whose intensities were adjusted with neutral density filters. An Iconix Model 6196 Power Supply was used to drive the lamps.

Each VEP was computed (by a PDP-12A LINC, Digital Equipment Company) as a waveform consisting of 125 data points representing a 500 msec period following stimulus onset. The 120 trials for each stimulus condition were subdivided into two sets of 60, so that a total of eight VEP patterns, 2 replicates for each of 4 stimulus conditions, were computed.

Reduction-augmentation was determined by measuring the slope of the linear regression line of the amplitude differences between two specific VEP peaks obtained in response to the four different flash intensities that were employed. Peaks were identified using the Hall algorithm. (Hall et al, 1973). Essentially the peaks involved were a major positive peak occurring at about 100 msec. and a major negative peak occurring about 140 msec. after stimulus onset.

RESULTS

Clinical changes over different periods of time in relation to the medication condition of patients while hospitalized are shown in Table 4. Those who were assigned randomly to chlorpromazine (N - 51) showed significantly greater clinical improvement between admission and discharge than did those assigned to placebos (N - 69; $p < .05$; t-test, one-tailed). This finding was reversed when clinical change between discharge and follow-up (personal contact cases only) was examined. Those who had been assigned to placebos (N - 39) while hospitalized showed significantly greater improvement than those who had been assigned to chlorpromazine (N - 37; $p < .05$; t-test, 2-tailed).

To check the possibility that, by chance, more disturbed patients had been

assigned to one medication than to the other, the severity of illness (SI) scores of those in the placebo and chlorpromazine groups (who had personal interviews at follow-up)were compared on the basis of their scores at admission (Day 2) and at discharge. In addition, SI scores at follow-up were analyzed. These data are shown in Table 5. Differences between medication groups on Day 2 and at discharge from the project are not significant. At admission both groups of patients, on the average, were moderately to moderately severely disturbed (i.e., had scores of between 4 and 5 on the seven point BPRS and GA scales). At discharge both groups had improved somewhat but, on the average, were still mildly to moderately disturbed (i.e., had scores between 3 and 4 on the BPRS and GA scales). At follow-up, however, the pathology of those who had been assigned to placebos was significantly less than those who had been assigned to chlorpromazine while hospitalized (1-tailed t-test).

It was observed also that between admission and discharge among those assigned to chlorpromazine 78% (40) showed clinical improvement and 22% (11) became worse clinically. For those assigned to placebo 57% (39) improved and 43% (30) became worse. These differences between those off and on chlorpromazine are significant ($X^2 = 6.258$, $p < .02$). When the data between discharge and follow-up were examined in the same manner it was found that for those assigned to chlorpromazine while hospitalized 57% (21) showed improvement and 43% (16) became worse. For those assigned to placebo while hospitalized 79% (30) showed improvement and 21% (8) became worse. These differences are significant ($X^2 = 4.242$, $p < .05$). In other words for the young acute schizophrenic males investigated in this study there is a short term beneficial effect of chlorpromazine within a hospital context but this does not hold over time. In the long run, most patients <u>not</u> given phenothiazine medication do better clinically.

Length of hospital stay was not significantly different for patients assigned

to chlorpromazine and placebo (means of 42.4 vs 45.0 days respectively; the median number of days were 24 and 34). Of the total sample of 127 patients, 43% (54) were discharged after less than one month of hospitalization.

Data were examined also in terms of patients' combined medication condition while hospitalized and at follow-up. A further breakdown was made in terms of premorbid history and paranoid-nonparanoid diagnoses at admission. These data are shown in Table 6 with t-test results shown in Table 6A. It can be seen that patients showing the greatest improvement (highest CI scores) were those in the PL-Off group (i.e., those randomly assigned to placebos while hospitalized and who reported they were off antipsychotic medication at follow-up). Of particular interest is the finding that they showed significantly greater improvement than those in the CPZ-Off group (i.e., those randomly assigned to chlorpromazine while hospitalized and who also reported they were off antipsychotic medication at follow-up).

The PL-Off group also showed significantly greater clinical improvement than patients who were either in the CPZ-On or the PL-On groups. The latter two groups were found to be significantly more disturbed at follow-up than those who were off medication at follow-up. Patient drug status at last contact was found to reflect post-hospital medication utilization throughout the follow-up period. For example of 78 personal contacts made during the follow-up period among those in CPZ-On group (N - 22) 77% of the time individuals reported they were taking antipsychotic medication. Of 88 personal contacts made with those in the PL-Off group (N - 24), 18% of the time individuals reported they were taking antipsychotic medication. It was noted, however, that 17 out of 24 patients reported they were not on medication at any time they were contacted.

It can be seen from Table 6A that the difference between the PL-Off and the CPZ-Off groups of patients is found primarily among those who showed good premorbid

histories and those who showed paranoid characteristics at admission.

Rehospitalizations were also examined and these data are shown in Table 7. Those in the PL-Off group had the fewest rehospitalizations (8%); this can be compared with those in the CPZ-Off group where more individuals experienced rehospitalizations (47%). The PL-Off group of patients also showed fewer rehospitalizations than those either in the CPZ-On group (73%) or the PL-On group (53%). Looked at in a slightly different way it can be seen from Table 8 that significantly fewer patients assigned to placebos while hospitalized were rehospitalized later compared to those who were assigned to chlorpromazine ($X^2 = 7.616$; $p < .01$).

A comparison of overall functional disturbance (OFD) scores at follow-up for patients off medication at follow-up also was undertaken. Those who had been assigned to placebos while hospitalized showed significantly less functional disturbance ($M = 1.71$, $SD = 1.146$, $N = 21$) than did those who had been assigned to chlorpromazine ($M = 3.25$, $SD = 1.682$, $N = 20$; $t = [illegible]7$, $df = 39$, $p < .002$). OFD scores were not significantly different either at admission or at discharge from the hospital portion of the project.

Patients who had a marked reduction slope (i.e., - 2.50 or less at admission) showed the greatest clinical improvement between admission and follow-up as shown in Table 9. Five out of 10 (50%) were in the PL-Off group while the remaining five were distributed among the other three drug conditions. These extreme reducers showed significantly greater clinical improvement than did either extreme augmenters or those with intermediate slope values. Of these 10 extreme reducers 3 were on phenothiazines at admission and seven were not.

The data were analyzed also in terms of those who displayed at admission either paranoid or nonparanoid characteristics on the BPRS (based on grandiosity, hostility and suspiciousness items). No significant correlation was found between paranoia

and slope score. Among reducers, those who showed paranoid characteristics were significantly more disturbed (severity of illness score of 1.95, SD .487, N - 8) at admission than those who had nonparanoid characteristics (SI score of 1.15, SD .544, N - 12; $t = 3.178$, $df = 18$, $p < .01$). No difference was found between paranoid and nonparanoid individuals who were augmenters. Since the significant clinical change between admission and follow-up among the paranoid reducers might be attributable to the fact that they were more disturbed at admission and therefore had "room" to show greater clinical improvement over time, severity of illness (SI) scores obtained at admission and at follow-up were examined for these groups also. At admission reducers with paranoid characteristics were more disturbed than augmenters with paranoid characteristics. The difference approached significance ($t = 1.923$, $df = 14$, $p < .10$). At follow-up, reducers with paranoid characteristics were less disturbed than augmenters with paranoid characteristics but the difference was not significant ($t - 0.947$, $df = 14$). No similar trends or differences were found for patients with nonparanoid characteristics. In other words the data suggest that patients most likely to show the greatest clinical improvement, independently of whether or not they are on phenothiazines at the onset of their acute schizophrenic episode, are patients who are reducers showing paranoid characteristics.

Since individuals with paranoid characteristics that were not given medication when hospitalized did better long term and since this finding does not correspond to previous reports of Goldstein (1970) Judd et al (1973) and Evans (1973) who reported better outcome among nonparanoid schizophrenics with good premorbid histories who were not given medication, it was decided to examine post hoc the persistence of paranoid symptoms. For this, BPRS ratings of hostility, grandiosity and suspiciousness were used. Ratings of ideas of reference could not be used since it was subsumed under ratings of unusual-thought-content and overall-thought-disturbance and documentation of ideas of reference were not always specifically recorded. The

BPRS was used rather than the Venables & O'Connor scale since the latter was completed only once, at admission, whereas repeated BPRS ratings were made throughout the in-hospital and post-hospital phases of the study. It was found that the three BPRS items used to assess paranoia correlated .67 with the Venables & O'Connor scale.

The persistence of paranoid ratings is shown in Table 10 for patients in the follow-up sample on whom data were available. It can be seen from Table 10 that 52% (15/29) of the patients rated as paranoid at admission converted to a nonparanoid status by time of discharge and 78% (25/32) had converted to a nonparanoid status by their last follow-up interview. Among those initially rated as nonparanoid at admission only 16% (7/45) were rated as paranoid at discharge and 15% (7/47) at their last follow-up contact. There were 48% (14/29) who appeared paranoid at admission and who were still paranoid at discharge; 22% (7/32) were still paranoid at their last follow-up contact. On the basis of these findings it appears that, among individuals of the type selected for this study, most of those who show paranoid characteristics at admission ultimately lose these characteristics and convert to a nonparanoid status. Most of those who show nonparanoid characteristics at admission (N - 48) retain those characteristics, 84% (38/45) being still rated as nonparanoid at discharge and 85% (40/47) at follow-up.

DISCUSSION

Emerging from this study is further evidence that there is a subgroup of acute schizophrenics who do well long term without the use of phenothiazine medication. The PL-Off group of patients (assigned to placebos in the hospital and found off phenothiazines at follow-up) showed significantly greater clinical improvement and less pathology at follow-up, significantly fewer rehospitalizations and significantly lessoverall functional disturbance in the community than any other group of patients, including those in the CPZ-Off group. Also, significantly fewer patients in the placebo group became worse in the period from discharge to follow-up.

These findings are in general agreement with the observations of other clinicians and investigators that there is a small group of schizophrenics who recover and continue to do well without the continuous use of phenothiazines. Kraepelin as reported by Lehmann (1967), noted that 13 percent of dementia praecox patients recovered without deterioration or major defect in an era before the discovery of antipsychotic medication. Similarly Lehmann (1967) states that permanent and complete recovery from a schizophrenic break occurred in 2 to 4 percent of the schizophrenic population prior to the introduction of neuroleptic drugs and indicated the percentage would be somewhat greater if one included those "with social remission with personality defects or full remission with further relapses." More recently Goldstein (1970), Judd (1973) and Mosher (1974) have also reported results indicating some schizophrenics do as well or better than similar patients who are given antipsychotic medication.

A considerable body of literature, however, stresses the finding that phenothiazines are effective in the treatment of most schizophrenias. In this study also, at least between admission and discharge, those who received chlorpromazine showed a faster and greater improvement than did those who received placebos. The result requiring interpretation is the long term opposite outcome difference between the groups placed on chlorpromazine or placebo while hospitalized.

Before interpreting our findings, limitations of the study should be mentioned. Results were neither replicated nor cross-validated and thus may represent chance rather than real effects of the variables that emerged as significant. There was lack of objective data on whether or not individuals actually were or were not taking antipsychotic medication at last follow-up contact. It would have been desirable to run FPN tests throughout the follow-up phase of the study but this was not feasible primarily because of manpower limitations. Similarly it would have been desirable to assess the psychosocial dynamics of the ex-patient's living environment to determine if, by chance, the group showing the greatest clinical improvement lived in a better milieu than did other study subjects. However, when type of living situation was evaluated (that is, living alone, with family, with friends etc.) no differences were found.

On the basis of the results reported it becomes important to ask the following questions: Why is routine and continuous use of phenothiazines contraindicated for some schizophrenics? How can such cases be recognized? How should they be managed?

There are a number of considerations that are relevant to the first question. It may be that the period immediately following an acute schizophrenic break is critical and how the patient is treated then is quite important. A number of observers have suggested that the stormy phases of schizophrenia can be looked upon as an attempt at reorientation and solving problems of living (Boisen, 1942; Jackson and Watzlawich, 1963; Shakow, 1971; Soskis and Bowers, 1969; Bowers, 1965). Boisen (1942) indicated that in the acute schizophrenic episode "there lies a problem to be solved ..... there is an attempt at reconstruction that may or may not succeed."

In other words, in order to solve problems of living the acute schizophrenic, in many instances, needs to retain his sensitivity and awareness and must have full

access to all his psychological resources. Reports by Goldstein (1970), Goldberg (1965), Hollister (1964), Margaro and Vojtisek (1971) Rappaport et al (1971) and others (Heninger, Dimascio and Klerman, 1965; Silverman, 1972, 1974) cited earlier suggest there are negative effects, such as decreased sensory and psychological sensitivity, and decreased problem solving ability, associated with the use of phenothiazines in some schizophrenics. The occurrence of negative psychological effects related to the use of antipsychotic medication are phenomena that are not as easily observed as negative behavioral effects. Consequently, they can be readily overlooked in any health care system that is not geared to obtain adequate feedback on the psychological and cognitive functioning of those being treated. Also, the effects of medication on various functional criteria - which may be considerably more germane to long term post-hospital survival than changes in certain kinds of overt behavior while hospitalized (such as overactivity, hostility, emotional inappropriateness) - frequently cannot be judged adequately during short term treatment or inpatient care.

The answer to the second question - how can patients be recognized who will benefit from not receiving phenothiazine medication routinely and continuously - is elusive and cannot be answered with precision. It would appear from present data that these patients are most likely to be found among young males at the onset of their first or second acute schizophrenic episode. (No factual comments can be made about females since they were not included in the study but the same criteria might hold for them.) These patients are also more likely to be found among those with good premorbid histories and among those who show paranoid characteristics at the onset of their break. They may also show a perceptual style reflected in an extreme reduction reaction in their visual evoked response. The latter finding is in need of replication, particularly since augmentation-reduction slope measurements appear to be somewhat fragile methodologically; that is, slight variations

in procedure used to identify VEP peaks from which slope values are obtained do not yield similar results. Only in about 37 percent of the cases examined (18 out of 49) was there close agreement when related methods of peak identification were employed (NIMH Report, 1974).

In another article, one of the authors has put forward theoretical considerations of why some reducers may be poor candidates for phenothiazine treatment (Silverman, 1974). Basically he postulates that psychotic reducers are hypersensitive to stimulation and their reduction (attenuation) of incoming stimuli is a defensive maneuver to prevent becoming overwhelmed by information which they cannot differentially filter so as to separate relevant from irrelevant material. Also Silverman postulates that the reduction maneuver provides a protected 'space' within which problem-solving activities can be completed. Phenothiazines, by reducing neurological sensitivity (Rappaport et al, 1971) (Killam and Killam, 1959), may interfere with the problem solving or reintegrative processes that must occur in some schizophrenics.

On the issue of premorbid history, our finding is that of all patients off chlorpromazine in the hospital those with good premorbid histories as compared to those with poor premorbid histories are more likely 1) to remain off medication after discharge 2) to show the greatest long term clinical improvement 3) to have the least pathology at follow-up and 4) to show a lower number of rehospitalizations. These findings are consistent with other reports dealing with outcome in these types of patients (Goldstein, 1970; Evans, 1973; Bromet, Harrow, Kasl, 1974). A good premorbid history suggests that an individual has some equity in life, has accomplished something (viz, educationally, job-wise, heterosexually, etc.) and consequently has knowledge and familiarity with a standard and quality of life to which he can and may want to return. The individual with a poor premorbid history may not have equivalent experience or exposure. Similar findings and inter-

pretations have been reported by other workers (McCabe et al, 1972; Vaillant, 1964; Zigler and Levine, 1973).

With respect to paranoia our results indicate that of all patients not receiving chlorpromazine while in the hospital those rated as paranoid were significantly more likely to remain off medication and to show the greatest clinical improvement. Other clinical observations and reports also suggest that some paranoid individuals do well off medication long term. For example Goldberg, Schooler and Mattson (1967), on the basis of their results, speculated that "after five weeks of treatment one might predict that ..... the placebo effects on paranoid symptoms might equal or perhaps exceed drug effects." Kellam et al (1967) was cited as suggesting "that paranoid symptoms respond to placebo treatment ..... because these are learned behaviors and, therefore, can be unlearned ....." Paranoid ideation is frequently "localized", that is, some paranoid individuals can function well except when circumstances intrude upon their area of paranoia. Functional deficits in the nonparanoid individual are usually more wide spread. Consequently it seems reasonable to expect some paranoid individuals to show a better functional outcome than some nonparanoid individuals. Also, as suggested by our analysis, it is likely that at times of acute exacerbation of schizophrenia some individuals demonstrate only a short-lived type of paranoia and this would augur well for recovery. The lack of persistence of paranoid symptoms may be a clue to identifying those who can show marked and persistent long term overall clinical improvement with the use of little or no phenothiazines. The findings of Freedman, et al (1967) are relevant here. They found that paranoid schizophrenics most likely to show symptom reduction within three months were those who met two out of the following three criteria; showed low cognitive differentiation (that is, showed amorphous-distorted Rorschach responses); displayed high social isolation; and displayed low oppositionalism (that is, low amount of verbal orbehavioral abusive acts).

In disagreement with the findings of this study are reports supporting the idea that some paranoid schizophrenics do better on phenothiazine medication (Goldberg, Klerman and Cole, 1965; Goldberg, Schooler & Mattson, 1967; Klein, D.F. - personal communication December 1973). In further disagreement are reports by Goldstein (1970) and Judd et al (1973). They found that schizophrenics who did best off phenothiazines were those who not only had good premorbid histories but who were nonparanoid clinically. Perhaps the difference in results may be related to differences in sample populations or methods of diagnosing paranoia (viz, hospital diagnosis in their studies, Venables & O'Connor criteria in ours). Goldstein (1970) did not describe his sample in terms of age, acuteness of illness at time of testing or whether a patient was experiencing only a first or second schizophrenic break.

Further investigation needs to be undertaken on relationships between paranoia and the effectiveness of phenothiazine med cation. New ways will have to be sought and more care will have to be taken to define subject populations b eing studied. The possibility that there are several types of paranoid schizophrenics needs consideration. Ratings of paranoia should probably not rely on hospital diagnoses but should be based on objective scales applied during personal interviews by trained researchers.

It remains a challenge to find ways of identifying patients who do better long term off rather than on phenothiazines, even though they represent a minority of theschizophrenic population. If such patients could be identified it would improve our diagnostic capabilities and increase our ability to choose the most effective treatment for each patient. Undoubtedly it would also contribute to a reduction in the incidence of drug induced complications such as tardive dyskinesia (Crane, 1973). These considerations are particularly important in the light of the development of community mental health programs where there is emphasis on routine

and long term use of phenothiazines as well as emphasis on brief hospitalization - perhaps too brief in some instances (Glick 1974).

The third question - how to manage patients for whom phenothiazines or other antipsychotic medications are contraindicated - may be answered in part by procedures employed in this study. It may be important to establish a treatment milieu with carefully selected personnel who are able to tolerate bizarre behavior without routinely calling for medication; who are able to accept the acute schizophrenic episode as a period in which some schizophrenics have the opportunity to reintegrate and to return to a mode and level of functioning that is compatible with survival in our society; and who are able to remain supportive under difficult conditions. A more detailed description of the treatment milieu employed in this study has been presented elsewhere (NIMH Report, Section VI, March 1974).

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TABLE 1

PATIENT CHARACTERISTICS (N - 127)

| Age | | | Diagnosis | | Premorbid Hx, | | No. of Previous Hospitalizations | | |
|---|---|---|---|---|---|---|---|---|---|
| 16-25 | 26-35 | 38 | Par. | Non-Par. | Good | Poor | 0 | 1 | 2+ |
| 103 | 22 | 2 | 63 | 64 | 81 | 46 | 63 | 31 | 33 |

| Drug Status on Adm. to Project | | Marital Status | | | | Education Level | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| On Major Trang. | No Drug | Sing. | Marr. | Div. or Sep. | Wid-owed | <H.S. | H.S. Grad. | Some Coll. | Coll. Grad. | No Data |
| 53 | 74 | 105 | 16 | 6 | 0 | 27 | 34 | 54 | 11 | 1 |

| Ethnic Group | | | | | Occupational Category | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cauc. | Orient. | Negro | Mex. Amer. | Amer. Indian | Prof. Tech. | Mgr. Bus. | Cler. Sales | Skill; Semi Skill | Un-Skill. | No Past Emp. | Stud. | No Data |
| 111 | 5 | 6 | 4 | 1 | 4 | 3 | 1 | 24 | 40 | 21 | 30 | 4 |

| Employment Status at Admission | | | |
|---|---|---|---|
| Employed | Unemployed | Student | No Data |
| 21 | 73 | 30 | 3 |

TABLE 2

LENGTH OF HOSPITALIZATION AND DRUG ASSIGNMENT

| DAYS | 1 - 14 | | 15 - 30 | | 31 - 60 | | 61 - 90 | | > 90 | | NO DATA | | TOTAL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| All Patients | 36 | 29 | 18 | 14 | 22 | 17 | 9 | 7 | 38 | 30 | 4 | 3 | 127 | 100 |
| Placebo Patients | 20 | 27 | 7 | 9 | 15 | 20 | 6 | 8 | 24 | 32 | 2 | 3 | 74 1/ | 100 |
| Chlorpromazine Patients | 16 | 30 | 11 | 21 | 7 | 13 | 3 | 6 | 14 | 26 | 2 | 4 | 53 1/ | 100 |

1/ These numbers coincidentally are the same as those in Table 1 showing the number of patients on and off antipsychotic medication upon admission to the study, but patient compositions differ.

TABLE 3

LENGTH OF TIME IN FOLLOW-UP, REHOSPITALIZATIONS, RESIDENCE, AND EMPLOYMENT STATUS AT LAST FOLLOW-UP CONTACT

| Length of Time in Follow-Up (Months) | N[1] (108) | NO. OF REHOSPITALIZATIONS | | | | | PLACE OF RESIDENCE AT LAST CONTACT | | | | | | | | | | EMPLOYMENT STATUS AT LAST CONTACT | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | Still in Hosp. | Parents | Friend | Spouse | Alone | Commune | Boarding House | Psychiatric Hospital | Halfway House | Prison | Other | Hospitalized | Unemployed | Employed | Student | Prison | Other |
| 36 | 2 | 2 | | | | | | | 1 | 1 | | | | | | | | | 1 | 1 | | |
| 30 | 5 | 3 | 1 | | 1 | | 1 | 1 | | 1 | 1 | | | 1 | | | | 2 | | 3 | | |
| 24 | 23 | 9 | 5 | 4 | 4 | 1 | 4 | | 3 | 5 | 4 | 1 | 4 | 1 | | 1 | 4 | 8 | 6 | 5 | | |
| 18 | 38 | 18 | 11 | 7 | 2 | | 12 | 3 | 3 | 5 | 1 | 3 | 3 | 5 | | 3 | 3 | 16 | 12 | 6 | | 1 |
| 12 | 33 | 22 | 8 | 1 | | 2 | 13 | 1 | 3 | 5 | 3 | 1 | 3 | 2 | 1 | 1 | 3 | 11 | 12 | 6 | 1 | |
| 6 | 4 | 2 | 1 | | 1 | | | 1 | | | 1 | | 1 | | | 1 | 1 | 1 | 2 | | | |
| 3 | 2 | 2 | | | | | | | | 2 | | | | | | | | 1 | 1 | | | |
| 1 | 1 | | | | | 1 | | | | | | | 1 | | | | 1 | | | | | |

[1] N includes information obtained on 27 individuals through mail or telephone contact only.

TABLE 4

CLINICAL CHANGE INDEX (CI SCORES[1]) IN RELATION TO HOSPITAL MEDICATION ASSIGNMENT

| | Random Medication Assignment While Hospitalized | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | | Chlorpromazine | | | | |
| PERIOD | M | SD | N | M | SD | N | t | p |
| Admission to Discharge 2/ | 0.29 | 0.521 | 69 | 0.47 | 0.527 | 51 | -1.866 | .05 * |
| Admission to Discharge 3/ | 0.36 | 0.500 | 39 | 0.54 | 0.521 | 38 | -1.537 | - |
| Admission to Follow-Up | 0.66 | 0.570 | 41 | 0.50 | 0.677 | 39 | 1.148 | - |
| Discharge to Follow-Up | 0.59 | 0.632 | 39 | 0.18 | 0.796 | 37 | 2.458 | .05 |

1/ CI scores based upon BPRS (OTD, OED, OFD scores) and GA changes over the periods indicated. Scores ranged between -1.00 and 1.00 where -1.00 indicates worsening on all four measures and 1.00 indicates improvement on all four measures.

2/ Ns do not equal 127 because of missing data.

3/ Includes only patients in follow-up who had personal interviews; Ns do not equal 81 because of missing data.

* One-tailed

TABLE 5

SEVERITY OF ILLNESS (SI SCORES[1]) AT ADMISSION, AT DISCHARGE AND AT FOLLOW-UP IN RELATION TO HOSPITAL MEDICATION ASSIGNMENT

| Evaluation Time | Medication Group: Placebo M | SD | N | Chlorpromazine M | SD | N | t | df[2] | p |
|---|---|---|---|---|---|---|---|---|---|
| Day 2 (Project Admission) | 4.26 | 1.084 | 41 | 4.32 | 0.972 | 39 | -0.245 | 78 | NS |
| Project Discharge | 3.69 | 1.328 | 39 | 3.60 | 1.156 | 37 | 0.323 | 74 | NS |
| Last Follow-Up | 2.47 | 1.511 | 42 | 3.08 | 1.699 | 39 | -1.689 | 79 | .05[3] |

1/ Mean of BPRS and GA Scores; 1 - no signs or symptoms of mental or emotional disturbance, 3 - mild disturbance, 5 - moderately severe disturbance, 7 - extremely severe disturbance.

2/ Total N less than 81 because of missing clinical data.

3/ One-tailed.

TABLE 6

DEGREE OF IMPROVEMENT (CI SCORES[1]) BETWEEN ADMISSION TO THE HOSPITAL PROJECT (DAY 2) AND LAST FOLLOW-UP CONTACT BROKEN DOWN BY HOSPITAL - FOLLOW-UP DRUG CONDITIONS, PREMORBID HISTORY AND ADMISSION DIAGNOSIS

| Drug Status In Hospital | Drug Status At Follow-Up | | All Pts.[3] | Premorbid History | | Diagnosis | |
|---|---|---|---|---|---|---|---|
| | | | | Good | Poor | Paranoid | Nonparanoid |
| PL[2] | Off | M | .92 | .92 | .92 | .98 | .85 |
| | | SD | .164 | .177 | .098 | .055 | .205 |
| | | N | 24 | 19 | 5 | 12 | 12 |
| CPZ | On | M | .48 | .74 | .11 | .53 | .45 |
| | | SD | .668 | .460 | .743 | .566 | .728 |
| | | N | 22 | 13 | 9 | 9 | 13 |
| PL | On | M | .29 | .26 | .32 | -.10 | .42 |
| | | SD | .704 | .757 | .653 | .714 | .655 |
| | | N | 17 | 8 | 9 | 4 | 13 |
| CPZ | Off | M | .52 | .57 | .40 | .47 | .64 |
| | | SD | .669 | .687 | .607 | .639 | .720 |
| | | N | 17 | 12 | 5 | 12 | 5 |

1/ CI Scores based upon BPRS (OTD, OED, OFD scores) and GA changes between Day 2 and last follow-up contact. Scores ranged between -1.00 and +1.00.

2/ PL - placebo; CPZ - Chlorpromazine.

3/ Between admission and follow-up N is 80 rather than 81 because of missing clinical data at admission for one patient.

TABLE 6A

t-TEST COMPARISONS BETWEEN GROUPS OF SCHIZOPHRENICS WITH DIFFERENT COMBINED HOSPITAL/FOLLOW-UP DRUG CONDITIONS

| Drug Status | | | | Premorbid History | | | | Diagnosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| In Hosp. | at FU[1] | In Hosp. | at FU | All Pts. | df | Good | df | Poor | df | Par. | df | Non-Par. | df |
| 1. PL-Off | vs. | CPZ-On[2] | | 3.040*** | 44 | 1.492 | 30 | 2.243* | 12 | 2.606** | 19 | 1.799 | 23 |
| 2. PL-Off | vs. | PL-On | | 4.090*** | 39 | 3.411*** | 25 | 1.884 | 12 | 4.875*** | 14 | 2.231* | 23 |
| 3. PL-Off | vs. | CPZ-Off | | 2.755*** | 39 | 2.048* | 29 | 1.692 | 8 | 2.676** | 22 | 0.885 | 15 |
| 4. CPZ-On | vs. | PL-On | | 0.829 | 37 | 1.705 | 19 | -0.604 | 16 | 1.576 | 11 | 0.110 | 24 |
| 5. CPZ-On | vs. | CPZ-Off | | -0.162 | 37 | 0.710 | 23 | -0.687 | 12 | 0.234 | 19 | -0.479 | 16 |
| 6. PI-On | vs. | CPZ-Off | | -0.921 | 32 | -0.883 | 18 | -0.203 | 12 | -0.567 | 14 | -0.598 | 16 |

1/ FU - Follow-up
2/ PL - Placebo; CPZ - Chlorpromazine
* P<.05
** P<.02
*** P<.01

TABLE 7

REHOSPITALIZATIONS IN RELATION TO HOSPITAL/FOLLOW-UP MEDICATION CONDITIONS

| | Number of Patients Within Each Group That Was Rehospitalized | | |
|---|---|---|---|
| Medication Group On Project And At Last Follow-Up Contact | N | Patients Rehospitalized | Percent Rehospitalized |
| PL - Off | 24 | 2 | 8% |
| CPZ - On | 22 | 16 | 73% |
| PL - On | 17 | 9 | 53% |
| CPZ - Off | 17 | 8 | 47% |

TABLE 8

NUMBER OF PATIENTS REHOSPITALIZED IN TERMS OF THEIR INITIAL HOSPITAL MEDICATION ASSIGNMENT

| | | Rehospitalized | Not Rehospitalized |
|---|---|---|---|
| Randem Drug Assignment While Hospitalized | Placebo | 12 | 30 |
| | Chlorpromazine | 24 | 15 |

$X^2 = 7.616$; $P < .01$

TABLE 9

CI SCORES[1/]
IN RELATION TO EVOKED POTENTIAL SLOPES[2/]

| | Evoked Potential Slopes | | |
|---|---|---|---|
| | Marked Reduction Neg. Slope | Flat Slope | Marked Augmentation Positive Slope |
| M | 0.94 | 0.50 | 0.51 |
| SD | 0.135 | 0.720 | 0.722 |
| N | 10 | 10 | 10 |

1/ CI scores based upon BPRS (OTD, OED, OFD, Scores) and GA changes over the periods indicated in the table. Scores ranged between -1.00 and 1.00, where -1.00 indicates worsening on all four measures.
2/ For explanation of slope see text.

CI SCORE DIFFERENCES BETWEEN THOSE WITH DIFFERENT
EVOKED POTENTIAL SLOPES: t-TEST RESULTS

| | Marked Augmenters | Those With Mid Range Slope Values |
|---|---|---|
| Marked Reducers | 1.757* | 1.803* |
| Those with Mid-Range Slope Values | 0.029 | |

* $p < .05$, one-tailed

TABLE 10

OCCURRENCE AND PERSISTENCE OF PARANOID (P) AND NONPARANOID (NP) CHARACTERISTICS[1/]

| | At Admission | At Discharge | | | At Follow-up | | | |
|---|---|---|---|---|---|---|---|---|
| | | N[2/] | P | NP | N[2/] | P | NP | |
| No. of Paranoid Patients | 33 | 29 | 14 | 15 | 32 | 7 | 25 | |
| No. of Nonparanoid Patients | 48 | 45 | 7 | 38 | 47 | 7 | 40 | |

1/ Based on BPRS summed ratings of hostility, grandiosity and suspiciousness, a subject was considered paranoid if he had a score of ten or greater. Each item was rated on a seven point scale from not present (1) to extremely severe (7).

2/ N less than shown under At Admission because of missing data.